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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

SCIENCE BOARD MEETING

9:10 a.m.

Friday, November 16, 2001

Conference Room 1066
5630 Fishers Lane
Rockville, Maryland

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PARTICIPANTS

Science Board Members

Marion W. Anders, D.V.M., Ph.D.
Michael P. Doyle, Ph.D.
Owen Fennema, Ph.D.
Robert S. Langer, Sc.D., Chair
Robert M. Nerem, Ph.D.
Cecil M. Pickett, Ph.D.
Jose Principe, Ph.D.

FDA Participants

Norris E. Alderson, Ph.D., Acting Senior Advisor for Science, FDA

Dennis Baker, Associate Commissioner for Regulatory Affairs, FDA

Celeste F. Bove, CCC-A, Acting Executive Secretary, Office of Coordination and Communication

David W. Feigal, Jr., M.D., M.P.H., Director, Center for Devices and Radiological Health (CDRH)

Ajaz Hussain, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER

David Lepay, M.D., Senior Advisor for Clinical Science, FDA

Joe Levitt, Director, Center for Food Safety and Nutrition (CFSAN)

Bernard Schwetz, D.V.M., Ph.D., Acting Principal Deputy Commissioner, FDA

Steven Sundlof, Director, Center for Veterinary Medicine (CVM)

Linda Suydam, D.P.A., Senior Associate Commissioner for Communications and Constituent Relations

Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research (CDER)

Kathryn Zoon, Ph.D., Director, Center for Biologics Evaluation and Research (CBER)

Invited Guests and Speakers

Frances Bruttin, PrincewaterhouseCoopers, Pharmaceutical Sector Team

Alexa I. Canady, M.D., Co-Chair, CDRH External Science Review Committee

Doug Dean, Ph.D., PricewaterhouseCoopers, Pharmaceutical Sector Team

Steve Hammond, Manager, Process Analytical Group, Pfizer

G.K. Raju, Ph.D., Executive Director, MIT Pharmaceutical Manufacturing Initiative

Norman Winskill, Ph.D., Vice President, Manufacturing, Pfizer, Inc.

Public Comment Speakers

Robert Chisolm, International Technology Manager, AstraZeneca

Gideon Kantor, Ph.D., personal statement

Nouna Kettaneh-Wold, Umetrics

Gabi Levin, Ph.D., Brimrose Corporation of America

Scott C. Ratzan, M.D., M.P.H., M.A., Editor, Journal of Health Communication

Svante Wold, Ph.D., Umetrics

AGENDA

P R O C E E D I N G S

CHAIRMAN LANGER: Good morning. I would like to call the meeting to order. My name is Bob Langer. I wanted to do two things. First, my major task is to remind all the Board members to pay Donna $8 for lunch during the break. And, secondly, I thought we could just maybe go around the table and introduce everyone just briefly.

DR. PRINCIPE: My name is Jose Principe. I am Professor of Electrical Engineering. My expertise is biosignal processing. I work at the University of Florida.

DR. PICKETT: I am Cecil Pickett. I am Executive Vice President of Research and Development at Schering-Plough Research Institute.

DR. FENNEMA: Owen Fennema, Emeritus Professor of Food Chemistry, University of Wisconsin.

DR. NEREM: Bob Nerem from Georgia Institute of Technology. I am Professor of Mechanical Engineering and Biomedial Engineering.

DR. CANADY: I am Alexa Canady. I am not

on the Science Board but was on the Review Committee, Co-Chair, and I am Professor of Neurosurgery at Wayne State University.

DR. DOYLE: I am Mike Doyle. I am Director of the Center for Food Safety at the University of Georgia.

DR. ANDERS: Greg Anders, now a Professor Emeritus of Pharmacology and Physiology at the University of Rochester.

DR. SUYDAM: I am Linda Suydam, FDA Senior Associate Commissioner for Communications and Constituent Relations.

DR. SCHWETZ: Bern Schwetz, Acting Commissioner of the FDA.

CHAIRMAN LANGER: I am Bob Langer. I am Chair of the Science Board and a Professor at MIT in Chemical and Biomedical Engineering.

DR. ALDERSON: I am Norris Alderson. I am the Senior Acting Director--I am Acting Senior Advisor for Science. I'll get it right. It's a good job.

[Laughter.]

MS. BOVE: I am Celeste Bove. I'm the Acting Exec. Sec. in the Office of Science.

MR. BAKER: I am Dennis Baker. I'm the Associate Commissioner for Regulatory Affairs.

MR. SUNDLOF: I am Steve Sundlof. I am the Director of the Center for Veterinary Medicine.

DR. WOODCOCK: Janet Woodcock, Director, Center for Drugs.

CHAIRMAN LANGER: Okay, so now I would like to turn this over to Bern Schwetz, who is the Acting Principal Deputy Commissioner, to make some introductory remarks.

DR. SCHWETZ: Thank you, Bob. I'm in the precarious spot of beginning to talk and my notes are still in my office over in the other building, which is a position I try not to get caught in very often.

Let me follow up from where Norris was going with his title. When the Science Board met last time, Liz Jacobson was still with us as the Acting Senior Advisor for Science, and in the meantime Liz has retired, and is still helping us

in some ways. But she is no longer in the position that she was in when we met last time, and instead Norris has agreed to come in and help in this regard.

Norris has spent many years in the Center for Veterinary Medicine, and in his most recent position--recent in the last 15, 16, 17 years--has been the Director of the Office of Research within the Center for Veterinary Medicine. And in consultation with Steve, who reluctantly agreed to let Norris out of CVM for a while, Norris agreed to come and fill this position as the Acting Senior Advisor for Science, and I am very happy to have Norris helping me in that regard.

There is another change that has been made within my immediate Office of the Commissioner that I want to update you on. Dr. Mac Lumpkin is now serving as the Acting Deputy Commissioner of the agency. Mac was in the Center for Drugs with Janet for many years, and more recently has served as the senior medical advisor to me during this time when I have been the Acting Commissioner.

So we have now given Mac a more permanent title, if you will, of the Acting Deputy Commissioner, so I am glad to have his help. It helps to have, when you're not a physician in charge of the agency, it's nice to have a physician as a right-hand person helping with the day-to-day running of the agency.

I also want to thank our two new members of the Science Board. Dr. Cecil Pickett, as he has already identified himself, is from Schering-Plough Research Institute, the Executive Vice President of Discovery Research, a cell biologist by training, and was on the Science Advisory Board of NCTR. And I had a conversation, a couple of conversations with Dan Casciano about the possibility of having Cecil work on the Science Board at this time, instead of on the NCTR Science Advisory Board, and Dan agreed. So, Cecil, we're very happy to have you with us.

And Dr. Principe is also new. We welcome both of you to the Board. A professor of electrical engineering, has an interest in

something that is important to a lot of us, computational neuroengineering. That is something that a lot of us have talked about in one way or another as it relates to drug research or a new approach for looking at the nervous system function. That is something that I'm hoping we will be talking about more as we go. So welcome to both of you.

I have in my notes to talk about where we are from the standpoint of a new Commissioner, not that I can bring you information, but in hopes that maybe you have some information.

[Laughter.]

Because while I don't think we're in a different position that we were several months ago, where names were being mentioned but there isn't any specific action. So as far as I am in this position, the agency is still stuck with me, and for how long we don't know. But at any rate, things continue as they have been.

I want to talk a bit about counter-terrorism and the impact of the recent two months

on the priorities and the operation and the activities of the agency. Everybody says things aren't the way they used to be. Things haven't gone back to normal. I can assure you that things haven't been very normal in the agency since then. And I'm not going to go into detail on anyone of these things, but I just want to kind of give you a flavor of the kinds of day-to-day issues that we've had and what has been consuming our time and energies at a time when we're trying to keep the usual business of the agency flowing.

We have very thoroughly reviewed the emergency preparedness plans that we have within each of the Centers, because they all have them, for dealing with emergencies that relate to the products that are in the domain of that particular Center. We have certainly spent a lot of time backing up the rest of the department and the other agencies from the standpoint of the availability of vaccines and drugs and medical devices, because whether it was the terrorist actions in New York City or anthrax since then, we needed to have

everything from blood to skin, drugs, vaccines.

Many of our products were out there and of concern in one way or another, so we spent a lot of time reviewing product security, and how would we know if our products were the subject of some terrorist action or not? To say nothing of the fact that we have an adequate supply in the event that they are needed in case of some action. So product security has been reviewed.

Food security has been a big issue, and a lot of us have spent time talking to the press, talking to the public, talking to the industry, communicating about where we are on food security as a possible means of terrorist action.

The threat of anthrax in our mail rooms had a major impact. It's one thing to talk about having drugs available for those other people who might be exposed to anthrax, but when we have anthrax that supposedly--we had the presumptive positives in five of our mail rooms. After routine sampling and culturing, the word came back that we had presumptive positives, and then there were many

days before it was confirmed negative.

Well, in the meantime our people, like others, were put on antibiotics, and thousands of questions, many hours spent in front of our employees trying to provide perspective and answer questions, and hope that we wouldn't get positive confirmed results back, and what were we going to do in the event that they did? So I think that was another test of our ability to deal with an internal emergency that certainly had ramifications on the outside, as well.

Again, the expertise that we have that comes into play at times like this, an example is the recent interest in the irradiation of mail as a way of getting rid of anthrax or some other organisms through the mail. And in the Center for Devices and Radiological Health we have the expertise to be able to help answer those questions. So our people have been in there with the Postal Service and the others on a daily basis trying to figure out, is that an effective and safe way, and what kind of operating conditions would

you have to have? What are the capabilities? Is it just flat surface letters, or is it boxes? How thick can something be?

Another wrinkle to this is, if we go into the irradiation of mail aspect, what about things, products that we regulate that are shipped in the mail? And that's everything from drugs to biologics to devices to food, a number of other things that end up going in the mail, that if it was irradiated, wouldn't be effective if you used it. So there are a whole bunch of other questions.

So then do we have to go back to the manufacturers and say, "In the event that your product is shipped in the mail, is it stable under these conditions?" And what do you have to tell the consumer to worry about? So it's amazing how many ripples come out of this kind of thing.

Some of this has translated into a supplemental budget that we have put in, and from the standpoint of the money that has been requested by the administration, of that $20 billion that is earmarked so far, we have a request for $106

million. $61 million of that would be used to help protect us against things that would be imported, so a lot of this would go to the field.

A lot of it has to do with food security, but Joe Levitt isn't getting it hands-on. It's really going to the field operations, so Dennis Baker and his people are the ones who will get a lot of this to help improve our presence at the border, as well as our presence, our capacity behind the border for doing the laboratory work that is increased in the event that we have activities at the border and have to do a lot of sampling. Or the domestic side of it, where in the event that we have to do a lot of sampling because of questions that have arisen from domestic supplies, that we need the capacity to be able to do the lab work that this kind of increased action drives.

So that's $61 of the $106 million, and the rest of it has to do with other parts of the agency where we're trying to increase the stockpiles, make sure we have the materials that are needed in the

stockpiles that CDC manages and the rest of the department manages for emergencies.

We have spent a lot of time in the product centers--we, I mean generously, the people who are in the product centers have spent a huge amount of time communicating with the manufacturers to be sure that products that are critical are in fact not only available but in a supply that would be sufficient to meet the needs that we might anticipate under emergency conditions, antibiotics and vaccines in particular, and the possibility that we would develop new capacity for producing vaccines. There have been a lot of discussions with the industry that hasn't been manufacturing vaccines, or at least the ones that we need for anthrax, smallpox, and so on.

So there has been a lot of discussion, and the pressure that we get to get out there and make it tomorrow and have it ready is one that is very difficult for us, because the last thing we want to do is to approve a vaccine that's coming from a new source, that isn't safe or isn't effective, and to

build up hopes only to find out that it wasn't what we thought and we may have created a worse problem than we hoped to solve.

So at a time when everybody wants to be protected right now and have everything in place, we are trying to make sure that in the event that we increase the capabilities for manufacturing or developing new products, that when they are made available, they are safe, but do it as fast as we can so that we are not seen as "business as usual" and there's an emergency and we stood in the way.

We of course have continued to raise attention to the fact that we have some pathogens in laboratories of ours, and so does the industry that we regulate that's developing vaccines and other products, and to get out and find out the security of all of those pathogens that could be of interest to somebody else. So that has been a focus of ours, and part of this money that I'm talking about goes to increase our own internal security.

And of course the amount of coordination

with other agencies, inside and outside the department, has consumed hours per day of a lot of us, just talking and being sure that we keep the Secretary informed, or other members of our department who are out in the press informed, or to be sure that as decisions are made on how we should deal with these kinds of issues, that the best thoughts are put on the table to help focus the discussion and make some of these decisions.

One of the things that we have developed internally as a result of this is what we're referring to, and the name isn't necessarily nailed down yet, but a new Crisis Management Center. Dr. Woodcock has agreed to help pull this together for us, so for now, Janet is detailed to the Office of the Commissioner and Dr. Steve Galson, who is her new deputy, is helping to run the Center from day to day, but Janet is nearby. But Janet is helping us develop a plan to have a Crisis Management Center.

The agency has decades of experience in dealing with emergencies. That is one thing that

has been part of our menu all along, because we have an average of two to three tampering incidents per week, and those tamperings might be anything from a hoax, some of them have been real, some of them have been not only real but very serious. And the possibility now on our mind is that you never know when a tampering--this has been true before, but especially true now--when one of those tampering incidents might be the beginning of a terrorist activity.

And because we see a lot of these on a day-to-day basis and the Centers are well-prepared to deal with food poisoning issues and other product tamperings, there is a threshold of that at which we need to engage as a whole agency, as we have for the anthrax, as opposed to the Center for Foods dealing with a food crisis that they have dealt with in a normal way all along and it doesn't come to the attention of the whole agency.

So this management center will help to keep us communicating and help to sort out those more routine variety of emergencies that the

Centers take care of all the time, as opposed to one that could rise to the level that the whole agency needs to deal with it and be prepared to work with CDC and maybe the USDA and EPA and other agencies. So we appreciate that Janet has agreed to help bring this center to fruition.

Let me switch gears now. We end up spending a lot of our time talking about terrorism and preparedness for it, but I want to talk about some other things, too.

Peer review. The CDRH peer review has been completed to the stage where Bob and Alexa are going to comment on the review that has been done of CDRH. We are happy to see that this has been a productive process, and Dr. Feigal is going to respond to the comments that will be made.

We continue to talk to Dennis in the Office of Regulatory Affairs, with the expectation that a review of ORA--because of the science within the field operation--would be the next peer review, and then CVM and CDER will follow, so one-by-one we keep moving on this.

Just a very small comment on budgets from the standpoint of the 2002 budget. We are under continuing resolution. Both the House and the Senate have passed conference reports, and the agency is doing pretty well for 2002.

And we are pleased to know that we are receiving the pay increase, the salary increases as an item this year, as opposed to in past years having to take the required pay increases of our employees out of our operating budget. Well, this year the operating budget is there and, in addition, there is money for the pay increases, so that is a significant step forward. And if we had had that for the last five or six years, we wouldn't have been in the trouble we were programatically.

In addition, I mentioned the supplemental budget request of $106 million. That will help. One of the things that we realize is that while we have spent a lot of money on the food safety initiative in the last three or four years, a lot of the investment that we've made in food safety is

very important from the standpoint of food security, so it has been a good investment.

And it goes the other way, as well, so that as we get money for people at the borders, as we get more money to help with vaccines and drugs and what not, that helps, the security money helps safety surveillance and maintenance as well. So it isn't that we are investing in something that has a use only under those peculiar circumstances, so that's good for us.

We're working on the 2003 budget, but that is something that we will continue on for the next couple of years.

As I close, let me come back to Board members. Two of our members are here for the last time. In fact, only one of them is here. Dr. Marian Nessle couldn't be here today, but today is her last meeting. But in addition, Greg Anders is here as his last meeting this time, and I very much appreciate the help that both of you have been during this time. Greg helped me as a member of our Science Advisory Board at NCTR for a number of

years while I was still there, and I convinced him to come and be part of our Science Board here, as well. So, Greg, it has been a long time that you have committed your attention to us, and I really appreciate it, and thank you a lot.

In addition, I would remind you that over the next year--and please don't stand up and cheer when I say this--we do have more members whose term will be coming to an end, so I would ask you to be thinking about other colleagues of yours whom you would like to recommend as replacements, as we look at five new members coming on next year. So we can deal with that down the road, but be thinking of names.

Bob, I think I'll turn it back to you.

CHAIRMAN LANGER: That sounds great. Let me now turn it over to Norris Alderson to give us an update on the action items from the April 2001 meeting. Norris?

DR. ALDERSON: Thanks, Bob. Let me tell you that, first, I'm looking forward to working with all of you at the coming meetings, assuming

I'll be here. That is still an unknown. But I promise that the next time we meet, I will have the title correct.

I do want to remind you that Dr. Schwetz mentioned the two Board members, that this would be their last meeting, we have selected two members to replace them and I want to tell you about those.

First is Dr. Jim Riviere. He's from the College of Veterinary Medicine at North Carolina State University, and he's a veterinary pharmacologist. The second is Dr. Josephine Grima, who is Director of Research and Legislative Affairs for the National Marfan Foundation. Her expertise is in biochemistry, molecular biology, and cell biology.

Another little update is, I'm sure all of you remember Sue Bond. I'm glad to tell you that Sue and Rod Bond are the proud parents of a baby girl born in October, and so Sue is out on maternity leave at this time, and she will be back in February. In her absence, Celeste Bove, to my right, has been filling in extremely well, and I'm

extremely proud of the fact that we've had the staff to fill in behind Sue.

Two other people I do want to recognize that have helped in this, and that's Donna Mentch and Monica Spence. And particularly Monica today, if you've got problems with travel and things like that--I already heard one person that needs some help--Monica can help you take care of those problems. She will also be dealing with you in getting your reimbursement for your expenses, so don't forget that.

Now, an update from the last meeting. Bern has mentioned the peer review, so I won't mention that anymore. One other suggestion that came out of the April meeting was that we have an Ethics Advisory Committee, and remembering back, this came up in a discussion, I believe by Dr. Zoon, on tissue engineering and cloning.

The leadership council of the FDA has looked at this and decided to establish a list of ethicists that we will maintain in the Office of Science Coordination and Communication for our use.

We looked at that and felt this was the best way to address it. So we took your consideration and we put something in place to have that for us when we need it.

The second item is, if you recall last meeting, Dr. Skulnick made some comments regarding institutionalizing our peer review system. Since he is not here today, we'd like to hold off on discussing that because I think he has a big interest in that, so we will bring that up at future meetings.

I do want to bring your attention to the upcoming FDA achievement awards. If you will recall, that's a process that you are the final determining body on who gets those awards. Our in-house review committee has completed their review of these. We will be forwarding to you in the next two weeks two candidates for each of the categories, and you'll get the opportunity to vote, I hope by December the 7th, on your recommendations for each of those awards.

These awards will be presented at our

Science Board in February. So this is very key to us. We've got a lot of good scientists in the agency. This is one way we are able to recognize those, and we think it's very important to them.

One final point. We communicated to all of you this summer about coming in early for one of the meetings to visit our laboratories. I think all of you responded to that in an affirmative way. You've told us before that you wanted to hear more about how we establish priorities for our research, and this is one way we can start that discussion with you, is with you going out to our laboratories and really talking to the scientists and the managers there to address this issue.

So this will require you to come in a little earlier. We would like to do this the afternoon before this meeting. So at the same time we've had to change the date of our April meeting because of a conflict with the Food and Drug Law Institute meeting. So we want you to respond back to us as soon as possible about your available dates, April and May time frame. If we don't hear

from you shortly, we will take the initiative to get back to you.

So that's my comments, Bob.

CHAIRMAN LANGER: That's terrific, and very concise. That's very helpful. Thanks a lot.

Well, I think we've got a very exciting morning ahead of us, and the issue that we're going to discuss is the emerging science issue of pharmaceutical manufacturing, and Janet Woodcock is going to lead that discussion. I'll really turn this over to her. Janet?

DR. WOODCOCK: Thank you. Good morning, everyone. If I can get the shift P--shift key? All right. Now, what else do you want me to do? You'll do it? All right.

While we're getting our audiovisual stuff working, what I want to talk about today, and the program we have put on, relates to science issues in the regulation of pharmaceutical quality. Now, pharmaceutical quality we think is really--it's the roots of drug regulation for the FDA. It was quality problems that, in the early part of the

20th century, that really led to the formation of the Pure Food and Drug Act, the Food, Drug and Cosmetic Act.

CHAIRMAN LANGER: Janet, microphone.

DR. WOODCOCK: Oh, microphone, sorry. Okay. That led to the formation of the FD&C Act eventually. There were improper constituents, there were impurities based on manufacturing and so forth that led to various tragedies.

Since that time, drug quality is really felt to be the basis of our findings of safety and effectiveness, because if the quality of the product fluctuates, the findings from the clinical trials of safety and effectiveness can't be relied upon to project into what the drug actually is. So this is a fundamental issue for the FDA, but we feel that is currently being challenged, and let me explain how.

How do we regulate drug quality right now? Well, I'm going to go over this a little bit because some of you may not really be aware of this. The pharmaceutical industry manufacturing

sector is extremely tightly regulated by the FDA. That's the first fact.

As most of you may know, before a product is approved by the FDA, before a drug product is approved, there has to be pre-review and approval of both the process, the synthesis, the manufacturing process and so forth, all the documentation that has been assembled by the firm, and aspects of the facility submitted. All of that is reviewed in a prior approval way before a new drug would get onto the market.

In addition, the facility is inspected by FDA inspectors and everything is gone through extremely carefully there. And once a drug is on the market, if there are changes to the product or the process, these usually have to be submitted to the FDA and reviewed prior to being instituted.

And in addition the ongoing manufacturing facility is subject to FDA inspection and has to conform to standards called Good Manufacturing Practices. And according to the statutory framework, that is supposed to be done at least

every two years, so every firm should be inspected by the FDA every two years.

So this scheme, which has been in effect for many decades, is how a pharmaceutical quality is currently regulated by the FDA in the United States. Now, we think, one of the reasons we are coming here today is that we think there are some issues regarding this.

The goal of regulating pharmaceutical quality this tightly is that the product be of the highest possible quality. In other words, that's why we do this regulation, to ensure the highest possible quality of the pharmaceutical products that are regulated, but we feel that we may not be totally achieving this goal in some ways.

We are seeing at FDA an increasing trend toward manufacturing-related problems. These include things like recalls. When there are manufacturing problems, it may disrupt manufacturing operations, and we may see shortages or loss of availability of important drugs. And this also can have, manufacturing problems or

issues can have a negative impact on getting new drug approvals out.

So that is one issue. Although we think the products now are of high quality, we will have some presentations today that discuss the fact that the pharmaceutical manufacturing sector may have low manufacturing and quality assurance process efficiency. And this is an issue because the cost of drugs is a real issue for health care in the United States, and this contributes, a lack of efficiency in this sector contributes to the cost.

Now, not a lot of people have talked about this. I don't think it's a real popular subject. So I think this may be a somewhat controversial set of presentations that you're going to hear this morning.

And, in addition, we find, we feel that innovation, modernization, and adoption of new technology in this sector has been slowed. And what do we base that assertion on? Well, we know that in other countries where products are manufactured not for the U.S. market, there has

been a more rapid introduction and adoption of new technologies of various kinds. And that might be for the same product that is actually manufactured for U.S. use where those technologies are not employed. And these technologies we're talking about usually lead to a better level of quality assurance.

Now, the final issue for us in the current system of how we regulate pharmaceutical quality is, it really does place a high burden on FDA resources. Our regulation of pharmaceutical quality is resource-intensive for the FDA.

We get about 4,000 supplements submitted yearly. These are what I talked about earlier. When a change is going to be made in the manufacturing process or in the product in some way, a supplement must be submitted to the FDA. Some of these have to be reviewed by us. Some of them are simply noted by us.

Our FDA inspectors are unable to meet, currently, the biennial GMP inspection requirement, so we are not in the plants every two years, as

Dennis very well knows. And unfortunately for the non-domestic industry--and globalization is causing a major shift, especially in the bulk drug manufacture, to overseas facilities all around the world--our presence is even less there.

And some of the cause of this is the financial issues that I think Bern and others have introduced the Board to, some of the financial challenges that the FDA faces. However, nevertheless, whatever the cause, the bottom line is, we are not in the foreign plants even as often as we are in the U.S. plants, which is much less often than we are required to be under the statute.

This graph just shows, from the previous 10 years, sort of the rate of increase of us getting these manufacturing supplements. You can see as we approve new drugs, very frequently they go through a lot of changes in the next few years. Especially with current drug development, where things may not be completely worked out or optimized at the time the drug goes on the market, we're seeing a lot of supplements filed, and I

think this reflects that. It also reflects the success of our generics program. We're getting a lot of generic drugs on the market, and they have a lot of manufacturing supplements filed to them.

Now, due to the efforts of our chemists in developing new guidance, many of these in recent years have changed from requiring pre-approval, where the firms have to wait when they submit these until they're approved by the FDA, they have changed to what we call changes being effected, where they simply can notify us. They simply can send in the supplement, notify us, and go ahead and implement the change. But nevertheless you can see this is an increasing burden for the FDA at a time we don't have additional resources to deal with this.

Now, how did this system--how did we get here? Well, this whole system evolved starting about 30 to 40 years ago, at a time when the sectors of industry, many of them, by no means universal, but there were parts of industry that really lacked rigorous manufacturing procedures, so

it was totally appropriate, the changes in regulation that were implemented at the time.

But more importantly than lacking SOPs, there was really--at that time the science had not advanced to the point where there was some predictability in what factors affect a formulation's performance, if you follow me. So it was really what I call sort of a "know nothing" approach. We know nothing about what impact a change will have on a formulation. Therefore, we must control and check everything, because we cannot predict, we cannot model what's going to happen if we make a change.

And subsequent to that, the science and technology base--and again, this is going to be controversial--it hasn't evolved as quickly as in other manufacturing sectors, and there are probably a number of reasons for that, which I'll go into a little bit.

Now, the standards that I referred to earlier, the Good Manufacturing Practice standards, which are the standards that we impose for

inspecting plants, process standards for manufacturing facilities, these are empirical standards. They are not scientifically based standards. And the reason for that, again, is that we didn't have the underlying science to be able to predict what factors were important.

Now, over the last 10 years, the Center for Drugs and the Center for Biologics have worked on the International Conference on Harmonization, which is a sort of international standards harmonization setting body that developed consensus-based standards in a number of quality areas. And most of these had to do with the review aspects, what we review in terms of stability, how you test for stability and things like that. So some of those may have a more modern science base to them, but nevertheless they were primarily consensus-based, based on the experience and standards of the three regulatory agencies, Japan, EU, and U.S., that actually were putting these standards together.

And finally, I have to mention this

because I think it's a very strong factor, why has the science base and technology base--and I see people nodding in the audience--not evolved rapidly like it has in other sectors, aerospace or, I don't know, computer chips or what have you?

Well, for the innovative pharmaceutical industry, the most important thing is to get the products on the market rapidly, and we all know that. Manufacturing is really an impediment, in a way, something that shouldn't get in the way of that happening.

And so the industry, in the face of this intense regulation, I think has been very risk-averse in introducing new technologies or in challenging the FDA standards, because the bottom line was to get the product on the market or keep the product on the market. And this has sort of played into, I think, the issues around adoption of new technologies.

Now, where are we now? That's how we got here. Where are we now? Well, you know, the drug discovery revolution, which I'm sure you all have

talked about quite a bit, has really increased the early pipeline, and there's really not that many barriers to developing candidates, molecular candidates, so there's a push at the very early part of the pipeline.

There are a lot of ongoing efforts in companies to improve how drugs are developed, the pre-clinical to early clinical paradigm, to move that along quickly. What we are seeing, I think, is that as the clinical drug development time shortens, as there is an emphasis on speed, there is less and less attention paid during the clinical drug development phase to formulation development, manufacturing process development.

Now, all of this we think is feeding into some of the issues I talked about earlier, some of the problems that we're seeing, so that we feel it's probably unlikely that the innovator industry will slow down drug development in order to get their formulations finished, and so forth, and perfect. So what we really think is needed is some innovation in manufacturing process R&D,

introduction of new technologies, so when these products come onto the market, we can all have confidence that they will perform reliably, and that innovation can continue to be incorporated into the manufacturing sector.

Now, the challenges for FDA in this regard are--and this is our challenge everywhere. It's our challenge in the clinical area and everywhere, in regulating an innovative industry. It's how do we encourage innovation while ensuring that the quality is maintained. That's one of our big issues.

We know, or we certainly all hypothesize, I think, that successful adoption of new technologies will actually improve overall quality of pharmaceuticals, and also probably efficiency, and you'll hear about this in the presentations. But how do we do that? How do we enable the introduction of new technologies while maintaining the quality standards? And this is the essential issue that we're dealing with.

In particular, in this case, how do we

successfully shift from empirical, the art of manufacture based standards, to science-based standards for manufacturing process quality? How are we going to do that? It's a huge challenge.

In addition, we need to try to further decrease reliance on pre-approval review and on the physical, actually getting in there and touching the product and the lines and so forth, not because that's a bad model, but in fact we don't have the resources to do it, and that has been clearly demonstrated over the last decade. We are not getting in there all the time. So what other ways can we use to evaluate quality? And, finally, how to recruit and train a scientific work force that would be proficient in the application of these new technologies.

Now, today's approach, what we're going to do, we're going to present the problem to you from a variety of perspectives and go into much more detail, and we're going to use Process Analytical Technology as an example of new technology. By no means are we saying that this is the only new kind

of technology that needs to be introduced, but we felt that we needed some firm example that people could look at to see what we were talking about, and so we'll be using some process analysis technologies as an example of the kind of new technologies that could be helpful.

Our speakers, we're first going to have Doug Dean and Frances Bruttin from PricewaterhouseCoopers talk about it. Then we're going to have G.K. Raju, who is from academia at MIT, their Pharmaceutical Manufacturing Initiative, so an academic perspective on the study of manufacturing processes. Norman Winskill and Steve Hammond from Pfizer are going to give you the industrial perspective from their point of view, and Pfizer has been adopting some of these technologies, not in their regulated lines but in other aspects of their R&D. And finally we'll have an FDA perspective from Ajaz Hussain, who is the Deputy Director of our Office of Pharmaceutical Science.

Hopefully, by presenting from these

various perspectives, you'll get a broad view of what the problem is and also some of the various approaches that we might take to this problem. For the Science Board specifically, we'll be asking you at the end of the day if you are able to support our approach and what your comments are on this approach. What resources, external, scientific, academic or whatever, what resources do you suggest we would draw on to bring this about, assuming you do support the approach? And, finally, are there additional aspects to the regulation of pharmaceutical quality that we should focus on, that we are not adequately highlighting in this presentation and approach?

So, with that, I'll call on the first speaker.

DR. ANDERS: Janet, do you have time for a quick question?

DR. WOODCOCK: Certainly. Go ahead.

DR. ANDERS: In your third slide, you--I'm trying to quantify the magnitude of the issue. So you talk about recalls and loss of availability of

essential drugs. Can you educate us a little bit, what's the magnitude of this problem?

DR. WOODCOCK: All right. Well, sometimes it's difficult for us to talk about these things, which is unfortunate. But I think even in the era of bioterrorism, for example, there are certain antibiotics and other drugs that used to be manufactured, that are in short supply or are not manufactured.

One of the contributing factors to not manufacturing drugs is that the process, it is felt it would be so expensive to bring those processes up to the modern standards, do all the validation and all the other work that is required to be done, that companies abandon the manufacture, abandon that product. And so we get into situations where we have more single-source manufacturers, where we have manufacturers, we have products where people abandon the manufacture.

DR. ANDERS: Is it 5 percent of the drugs that are recalled, or 50 percent?

DR. WOODCOCK: Oh, you mean what is the

relationship of recall to manufacturing problems?

DR. ANDERS: What's the magnitude of this problem? And then, again, the loss, I guess you just now addressed the loss of essential drugs that a manufacturer may say, "Well, I'm going to quit making this compound," and so we have one provider.

DR. WOODCOCK: Right.

DR. ANDERS: But what's the recall? What are recall numbers like?

DR. WOODCOCK: We can get you the numbers. They have been rising over the past few years, but that's only one aspect. Let us go through the entire presentations, set of presentations, because that's just one facet of this problem.

I'm not saying that manufactured pharmaceuticals are of low quality now. That's not really the issue. All right? But getting into problems that lead to recalls and other shortages and so forth, that represents a problem, a system problem, you know, and we are constantly dealing with that. We're dealing with shortages that are generated by different manufacturing problems. I

can tell you that we are constantly dealing with this. And I can't give you a figure, like how often it happens, but it's a constant theme that the FDA has to deal with.

All right, we'll move on to the first speaker.

DR. DEAN: Good morning, everyone. My name is Doug Dean. I am from PricewaterhouseCoopers. I'm based in Basel, Switzerland. And I am not an accountant.

You're going to get a double act this morning. I'm here with my colleague, Frances Bruttin. Together we have been working in the pharmaceutical sector for a number of years, myself for about 25 years in pharmaceutical manufacturing, and we're going to share with you some of the observations that we have had working with our clients all over the world for the last decade or so.

And I really like this image to start with, because I think it sums up where we're coming from. It's a combination of cost, time, and

regulation. Before we get into this, I'd like to just declare some biases here and make sure that you understand the perspective that we're coming from.

First and foremost, we're engaged by our clients to solve business problems. This typically means looking for ways to improve the way the business operates and generate greater return to shareholders. We've been doing this exclusively in the manufacturing sector, largely looking at new processes, new ways of working, and new systems to support those ways of working for the past decade or so, primarily focused on working with R&D based large pharmaceutical manufacturing organizations.

I think what we'd like to shortly talk to you about today are the perspectives that we have seen in the past decade and the conclusions that we're reaching, basically that the way things currently are in the sector and in the industry is something that can't be sustained going forward. I think we've already heard from Janet this morning a couple of comments about the state of

pharmaceutical manufacturing in general, and I'd like to emphasize that. Compared to other sectors, the capabilities and the state of pharmaceutical manufacturing is actually quite poor.

We are going to show you how the way that we traditionally go about measuring our performance in manufacturing actually hides the opportunity for improvement, and we need to consider some different ways to measure it. The infrastructures that we put in place to support the need for the regulations that we have to work within tend to be not very economically feasible.

So there's opportunities there for improvement, and that through the introduction of new technologies, but I think critical to emphasize, technologies that are not put in in isolation. And I would like to draw that point out very clearly today.

And we will conclude by showing you that there is a massive potential for win-win, both for the consumers, for the industry, and for the shareholders, chiefly through four different

aspects here. We're going to show you how we can reduce risk; increase the effectiveness of our ability to be compliant with the various regulations that we have to deal with. In so doing, we will show how it's possible to dramatically reduce cost in manufacturing; and by doing that, to give some increased return to the shareholders.

And these things combined together, then, are going to create a win for the regulators and the consumers and a win for the business, and we'll show you how these things are strongly linked.

I think it's important to understand the environment that we are currently working in. I mean, here big pharma. If we look at what has happened in the industry over the past 30 years, we've seen a dramatic decline in growth, from double-digit growth 30 years ago to what seems to be a level of growth in the market that's leveling out at about 6 percent per year. Every economist has got a different opinion, but when you talk to them, they are generally in agreement that the

industry will continue to grow in an environment of about 6 percent per year.

If we look at the total annualized return to shareholders over a five-year period, and look at that over the last number of years, it's been steadily declining. It's the investment from the shareholders that provides the capital to grow the business, to look for new products, so it's important that the shareholders do get a return. But I think it's important to draw out here that in this environment of reduced growth, there has been reduced return to those shareholders.

If we look in the engine room of the industry here, the innovation and the discovery and bringing to market of new drugs, we've seen a dramatic fall-off overall in the productivity in research and development. We as an industry are pouring tens of billions of dollars into research and development but we're getting less and less out of it, measured in terms of the number of NCEs or NMEs that are brought successfully to market each year.

When we are bringing new drugs to market, what we're finding is that over the past 30 or so years there has been a dramatic decrease in the window of opportunity that we have to get a return on that massive investment. So decades ago one could enjoy a window of therapeutic exclusivity on the order of years, but lately we've seen that shrinking down to a matter of months or even weeks. So bigger investments, market growing more slowly, less opportunity to make a return on those investments, emphasis on time, time, time, get to market more quickly.

When we look in more detail at manufacturing in general, and I would say this is across the board in virtually every dosage form, whether we're talking about active ingredients or secondary production, we generally see that the levels of asset utilization in the sector are very, very low, typically about 15 percent. But because of the way that we measure the way we use our assets, we often fool ourselves into thinking it's a lot higher, and I'll draw this out more clearly

for you later.

We tend as an industry to accept the fact that we're going to have to throw away 5 to 10 percent of everything that we produce, or we're going to have to rework it, and we plan it in.

It typically takes, in a new product introduction environment, a good deal of time to actually get the scaled-up commercial level processes effective, working to the levels that we would like them to work at, and this is taking far, far too long. And it's basically accepted, I would say.

And as we'll show you, very typical across the board to see a total cost of quality approaching 20 to 25 percent in some cases of period costs in a given pharmaceutical manufacturing plant, and this is accepted as being just the way it has to be in the business. So that's the environment that we find ourselves in.

Conclusions here is, it's tough and it's going to get tougher, so there's going to be an increasing, an intensification of competition

within the business for resources. So if we're asking for capital investment to improve manufacturing, well, R&D are asking for more capital as well, so we have to have and be able to demonstrate a very good return on that investment.

And I think the other key conclusion here is that manufacturing has been really regarded as a Cinderella function in the industry, the poor stepchild, and there has been a "cause no problems" mentality which has really led to what I can only characterize as benign neglect of the need for higher and better performance in manufacturing operations. Steven Wheelwright did a number of studies showing that manufacturing as a function has to stop being internally negative or internally neutral and become an external supporter to organization strategy. So manufacturing is going to have to contribute more than it currently is.

Now, when we start looking at why is it like this and where do the problems come from, we find that actually the problem happens downstream. It happens, begins to happen long before we ever

get to commercial-scale production. We find that processes are transferred into manufacturing that are in most cases not well understood, and in many cases are not capable at the scales that we have to manufacture at. They are capable in laboratory or at clinical scales but not at commercial scale.

We find that the emphasis and the focus on new product introduction has resulted in masses of data that are going into the CMC section, but somehow we are missing a lot of critical information that helps people to actually understand the processes to be able to operate them effectively in a production environment.

We have done a number of studies that have showed that long before we get to Phase III clinical trials, approximately half of the manufacturing costs are already locked in, and therefore we're not able to do anything about it in terms of reducing them when we finally do get to production.

And, finally, we find that there is little basis, little scientific basis to take a decision

to trade off the pressure to get a new compound to market more quickly, to trade that time off in exchange for maybe a month or two more to spend more time understanding the process in order to enjoy the benefits of increased quality downstream.

Just to give one example here, a client that we worked with a number of years ago, a very simple example, this is an emulsion product. The critical quality attributes relate to the size of the droplets in the emulsion, and it's measured in an in-line process environment by shining light through and looking at the degree of absorption of the light.

And there were some upper and lower control limits set on this process in order to get the emulsion the way that it should be. The usual validation studies were done, three batches at exactly the middle of the upper and lower bounds there.

The problem was, the process was not well understood, and in fact it had been noted earlier in clinical manufacturing that the function of

absorption as a function of the control parameter created a situation where we were actually out of limit in one of the quality attributes, but this was somehow not understood in transferring the process to manufacturing.

So we've now got a situation where we have a process in manufacturing, we've got an upper and lower control limit, we have operators who are doing their best to keep the process within those boundaries, but it's fundamentally flawed. Even though we're within those boundaries, we're still producing a product that does not meet its quality attributes and will have to be scrapped or reworked.

What we'd like to show you, and I'll turn over to my colleague France Bruttin here to take you through this, three key things here in order to start to address this problem.

One is that in looking at manufacturing operations, we need to clearly understand where the value-adding activities are and where the non value-adding activities are. We find that non

value-adding activities add cost and time but they don't add value to the product.

We'll take you through one or two examples that show how, as an industry, our traditional approach to measuring performance in manufacturing hides the potential to improve and reach higher levels of performance that we really need. So as a non-accountant, I can blame the accountants for this, and we'll take you through some of that.

And we'd like to show you some rigorous approaches that are being used in other industries to apply a more rigorous and scientific-based approach to determine the ability of a process to be right the first time.

I'll turn it over to my colleague Frances Bruttin now to take you through this. Frances?

MS. BRUTTIN: I think, building first of all on a point that Janet was trying to bring across, where she was saying that the manufacturing, the pharmaceutical manufacturing tend not to be taking opportunities of the new technologies and the innovation and bringing them

into their daily work hangs around them being adverse to change, hangs around them being afraid of bringing change into the manufacturing process because of the impact with the regulators and the amount of paperwork that they would have to go through, so they prefer to stay with today's inefficient processes and ways of working and continue to get the product out the door.

I think we are going to tell you a little bit today that it goes a little bit deeper than that; that in reality, within the basis of manufacturing, there are a lot of inefficiencies, there is a lot of emphasis on trying to test quality in and prove quality, whereas if we take a few steps back and go back to basics, there are some fundamental things that we can change, and we will get quality and regulatory compliance out as a consequence. So I'm going to take you through some of them.

First of all, if we look at what actually happens in the plants and we distinguish between value-added activities and non value-added

activities, this is an example of a dispensing process. The process actually takes three days to be completed. Of those three days, 1 percent of that time is actually value-added. That is the weighing of the material before it goes into the hopper or the dispenser. The rest of that time is dedicated either to transportation of material; scanning in bar codes. It's waiting while the QA come back with the results of the bar code. It's moving the pallets from one area to another area. So over three days, 1 percent of all that time is actually value-adding.

If we take all of the subprocesses that make up the process from the raw materials to finished goods, the actual value-added time as we go through dispension, granulation, compression, coating, and packaging, over a 35-day process, three days are actually value-added. And these are real numbers. These are numbers from the studies that we have done actually in the shop floor, on the factory floor.

To make it a little bit more realistic,

we've actually taken photos of where these delays can be observed. what we have here is, after dispensing, the material is actually stored. In this case it was actually in the alleyways between the various different rooms where the production processes were taking place. So here we have delays. They were staying here for maybe typically five or six days.

Work in process, again, waiting until the next piece of equipment was ready; waiting for results coming back from QA for the in-process controls. Again, all this material is captured, which has been held up; it's work in progress.

And a very typical photo of what turned out to be 100 percent inspection. There was a problem here with the blister pack, and so these ladies over three shifts for a period of two or three weeks did 100 percent inspection for a single batch. This is non value-added activities. This is not contributing to the quality of the product, and it's certainly not contributing to the health of the final patient.

If you measure what is actually value-adding and non value-adding, and the way we do this is through an activity-based analysis--so we look at what the people are actually doing, we're looking at what is happening to the product as it moves along the process--you can identify those processes that are not actually adding value, you can reconfigure them, and you can make a much more effective manufacturing process. The best we have seen is about 50 percent. That means the ratio between non value-added activities and value-added activities is 50-50. So in this example it is possible to go through the entire manufacturing process in 6 days as opposed to 35 days.

So value-added/non value-added is one aspect. The next aspect--and I have to say this is probably due to our colleagues accounting--is how we measure the effectiveness or the output of a factory. We use standard accounting methods. This is also driven by the various MRP systems that have been in place. We talk about standard costs. We talk about standard utilization.

This is typical of what you will see. For asset utilization, what is defined as the total availability of an asset? We have here 80 hours a week. That represents two shifts per day, and there is of course the scheduled downtime and the scheduled conversion time. But since the accountants know that there are traditional losses and other expected losses and delays and waits, then they also schedule in a certain amount of time that they know will not be operational. Because they schedule it in, it's planned in, so suddenly we lose visibility and transparency of it.

So the people who come later say, oh, well, the allocated operational utilization is set at X percent. That X percent has already taken in the fact that the actual equipment is sitting idle. And therefore if they hit 90 percent of that X percent, they feel they're doing a good job.

If we look in reality at what is happening--and remember these assets that we have, we have capital investors in those assets, so those assets are alive, let's say, 24 hours a day, 7 days

a week, 365 days a year. So when we're calculating asset utilization, we should be calculating it on that basis. So instead of it being 80 hours a week, it's actually 160-hour-a-week availability.

If we then look, we find out that we have quite a high percentage which is unscheduled downtime, so downtime due to problems on the line, due to problems on line switch-over. Then we have operational time losses which are due to, in some cases to poor planning; to delays, again, delays with suppliers, delays with other material coming in. And then which I think is actually quite sad, when we look at what we're doing with our machines, we're actually spending quite a significant amount of time producing scrap, i.e., all those batches that do not meet the quality control that we've set on them, or reworking that scrap.

So at the end of the day, the actual effective up time is actually a very, very small percentage. From our studies this has come out to be around 15 percent asset utilization.

So we've looked at value-added versus non

value-added, we've looked at the difference between measuring for accountancy purposes and measuring for performance. So some people may be saying now, "Well, that's fine. I can blame the plant manager on all of that. This has nothing to do with our scientific approach to manufacturing."

Let's get to the main point. The main point is around the pharmaceutical process. We have been arguing that this process is not well understood. It's not well understood when it's transferred from R&D over into manufacturing. And what we have here is a way of measuring the processes, a way of comparing processes from one process to another. Obviously it's sigma. It's not rocket science. It's based on standard deviations.

It is a measure that has been used in various other industries. For example, if we start from manufacturing, Motorola and Siemens, around consumer electronics, but also in service industries, GE Capital, so for people who provide financial services, and also Caterpillar. So it's

a way of measuring lots of processes, not only the pharmaceutical process but all the processes, so the steps that people go through to support manufacturing, how people take those let's say manual steps, how they started, and how repeatable those processes are.

What this lets us do is see how well we are performing, see how repeatable our processes are through the plant. Obviously a higher sigma value indicates better performance. If we look here in terms of defects a 2 sigma process has around 300,000 defects; a 6 sigma process has 3 defects. This is what you may have heard about in terms of zero defects manufacturing.

If we see where the various industries are, semiconductors are between 5.5 and 6. Baggage handling in airports is a 4 sigma process. So where do you think pharmaceutical manufacturing is? Probably if I asked a CEO, he would tell me, "Yeah, we're somewhere between 4 and 4.5." Some people are saying uh-uh. We're actually about 2.5 consistently. Consistently 2.5.

Two ways of seeing this. You can measure the actual processes, and you come up with a 2.6, 2.5 measurement. Or you look at the cost of quality, or should I say the cost of poor quality. There is a direct correlation between the two, and as Doug had previously mentioned, we are all the time coming up with somewhere between 20 to 25 percent of period costs are costs that are related to poor quality, not only the costs for the QA and QC function, but it's the costs of rework, it's the costs of scrap, it's the costs of prevention appraisal, 25 percent.

Obviously everybody here understands standard deviation and sigma, but just very briefly, obviously there's two aspects that you're trying to control. One is the deviation around the particular process, between its upper and lower limits, so the spread. And the second is the ability to maintain the particular process between those limits over time, so the shift. So what you want to do is obviously keep the process with precision and with accuracy.

Now, if we take all of these together, what does this mean for the pharmaceutical manufacturer. Well, one point is, obviously it's unit costs. Taking these four together, we can have a dramatic influence on bringing down unit costs.

We start off by material costs. Obviously the reduction in scrap and waste, I think Doug mentioned is between 10 and 15 percent, so you can immediately reduce that down to I think somewhere--2 percent is the max in terms of scrap and waste.

With the reduction of non value-added activities, there is obviously a possibility to reduce the period cost. Part of this is reducing those costs of compliance, so reducing the amount of internal and external failures, and then once you are confident with the high level of quality you're getting out because you know your processes and they are highly capable, you can then reduce the amount of money that you're actually spending on prevention and appraisal.

On the other hand, your efficiency is

going up because you're increasing the process yield due to the less amount of scrap, and your plant volumes can go up. Why? Well, if we look at the argument around non value activities, previously that process was taking 35 days. It's now taking 5 days. If you can absorb the capacity, you can now do five runs in the time it was taking you to do one run previously.

So the net result of this, if you address these factors, is it's possible to significantly bring down the unit cost of production.

Let's shoot forward to , I don't know, five years, to the company that is performing, that's outstanding, that's leading terms of pharmaceutical manufacturing. They are operating at a 5 sigma level, so what does that mean?

Well, their quality and compliance costs are down to somewhere between 3 and 5 percent. The unit cost of production is 60 percent lower than the competitor's, who are still operating at 2.5 percent because they weren't at this presentation today. Cycle time has gone down to 5 days, so

obviously their productivity is up, their yield is up.

And this point, again, newly introduced processes are effective immediately. We saw again when Janet showed that slide with the number of supplements that were coming in, that's all the-- the process has been transferred from development into manufacturing, and then we tweak it. We get it a little bit better and a little bit better and a little bit better, and we blame those people in development because they didn't give us the right process.

What we're saying is, if you can use process capability and 6 sigma concepts already in development, so that you know that you understand the process, and the process is capable and is able to stay within the limits that you have set, you can pass this then on to manufacturing, who then know that from day one that process is effective. They can then do some fine-tuning, but you shouldn't be seeing all of these supplements because the fine-tuning is based on a statistically

stable process which development and manufacturing understand.

Key enablers to make this move? First of all, I think I would really like to focus on process understanding, understanding what is happening in the process. Second point is understanding the parameters that influence that process, those parameters that you are going to measure, those parameters that you are going to control to keep that process within the defined limits. The process capability hurdle is already in development to ensure that the processes that manufacturing get are actually effective and capable from day one. Obviously technology is a huge enabler in this area, as well.

And just some examples, we'll hear more later from my colleagues: Near infrared analysis of raw materials and in-process controls; continuous high-volume microwave sterilization; on-line measurement of variables, and supported by sigma tools, so you know exactly where your process is.

With these technologies there is also a need for encompassing enterprise technologies. So, for example, once you have all of these points, they need to be integrated into electronic batch records, so that again you're not wasting time waiting for the results to come back from QA or putting the whole batch record together manually. There is no point of having these technologies in place and then taking the paper results and pasting them into your batch record. And I won't even go near 21 C.F.R. 11 at this point.

And then finally, obviously, electronic document management solutions to enable you to share information between development and manufacturing. And, oh, yes, the thought of the manufacturing people being able to contribute early into the development of the CMC section, before it goes in for the submission, rather than achieving that as it's thrown over the wall from development and being forced to live with consequences of what happens in development.

So what's the upside of this? All of

those elements contribute to something which we call the compliance infrastructure, the organization, the people, the procedures, the policies in place to ensure compliance with internal quality management systems. Let's not forget that we're doing this to ensure the quality of the end product. And the second point of compliance is with the regulators.

What this can do is fundamentally shift the cost of compliance curve. What we see, the blue curve is where it is today in terms of your typical 2 sigma performance. By bringing in these new changes, you can move that curve down to 5 sigma performance, and you immediately get direct cost recovery but you also get a compliance gain.

What does this mean for the industry? Well, in a win-win situation the industry will be moving not only towards quality to meet the regulatory needs in terms of, if we take point 3, if that was the paradigm, then point 3 would be going straight up. But here what we want to do is a balance the need for quality and the need for

productivity. So in the move of moving from 3 sigma to 6 sigma in terms of doing the right thing right, we get quality and we get productivity, so we end up with a win for the regulators, a win for the consumer, and a win for industry.

So, to summarize, the industry needs to measure for productivity and not for the accountants. The solution is not just a collection of technologies. It's more complex than that,. And there is a win-win. The economics of compliance, where is the point on the cost of compliance where there is a win for the industry and a win for the regulators and the consumers?

Thank you.

DR. WOODCOCK: Perhaps we can hold questions as we go through, if that's okay with the Board. If you have specific questions, perhaps you would like to ask them now, or clarifications. Otherwise, we're going to have a long discussion period.

All right. Thank you. Now, the next speaker is Dr. Raju from MIT, and he is going to

talk about pharmaceutical manufacturing from an academic perspective.

DR. RAJU: I'm going to try to follow up on a number of things. What I'm going to try to summarize in the next half an hour or so is a set of research activities we have done within the MIT Pharmaceutical Manufacturing Initiative. We are a technology university and a business university, and so we try to use some of those skills to try to understand the opportunities and communicate them to society, the regulators, and the companies who fund a large fraction of our research.

The purpose of the Pharmaceutical Manufacturing Initiative is to describe and capture the opportunity to improve pharmaceutical manufacturing. Let me see what that means. What that means is, if this were the pharmaceutical industry, and the industry and the academicians are focused on many different aspects of it, we're going to choose to focus on this aspect of it. And really it's very rare to focus on that aspect, and that's going to be the subject of my talk for the

next few slides.

This is something that has been the course of many years of working, and we have had a chance to work with almost every brand name company, a large number of biotech, and some branded generic companies as well, and so over the years we feel we have had a reasonable set of experience base that makes us feel that maybe we can begin to make some conclusions.

We were very excited to start this manufacturing initiative at MIT, and if this was our goal, it seemed like a good place to start is to find out what pharmaceutical manufacturing really was. So we went around to the vice presidents of manufacturing, to the companies, to society, to each other, and said "What is manufacturing, what is this piece here?"

We were all excited. What we saw was something very different. What we saw was an organization that was told, "Don't be on the critical path." "You're not as important as R&D." "You're a cost." "Don't stock out." "Be sure you

do it the same way you told us for the next 12 years, and show compliance, and we'll come every couple of years to your plant when we can to see how well you're doing." And that's the investigators, as well.

From a society, from the rest of the organization, there was a message that says, "Just don't screw up." "You're a cost center." And I can't think of anything worst for somebody to tell me, because it means I don't add value to society. The vice president of manufacturing says, "How can I win?" And the definition of a win almost seems nonexistent.

The result of that shows up in the implementation of the technologies, and we'll show you some of the consequences and some of the opportunities of those technologies as we go forward. But if this was pharmaceutical manufacturing, then either starting this initiative at MIT was something we shouldn't have done, or maybe this problem, so-called defensive mind set, is really the opportunity.

And we said yes, that's what it is, let's try to understand why, let's try to understand the drivers of the system, let's get to the common things of science and technology, and then we'll change the results that come out of the system. We then brought a significant number of vice presidents of manufacturing, who all said "How can I win?" and said "Let's all get together. Let's begin to formulate a winning strategy."

This is for the MIT Sloane School of Management, which has a very leading management of technology program, the Department of Chemical Engineering, and the Department of Industrial and Physical Pharmacy. Although disputable, the Business School, Chemical Engineering School, and the School of Pharmacy are rated to be one of the best in their disciplines.

And we said, here is a set of vice presidents who are trying to figure out how they can win. Science we think should help society, and science could be a win-win situation. Let's begin to listen to their concerns. Somewhere along the

way, since this is a regulated industry, we will have to figure out what we do with the FDA, but let's keep them in the equation. Let's figure out what we want to do, what the opportunities are. And somewhere along the way we'll start talking to the FDA, when we feel we are ready, but we have said we've got to do it sometime. And I have been fortunate to be involved in all those three different disciplines through formal affiliations.

If that was that tiny little box that we call pharmaceutical manufacturing, and we all want to analyze it together to understand why it looks the way it is, let's standardize on a few boxes around that box. And if you think of pharmaceutical manufacturing as this 12 to 15-year process, sometimes more, sometimes less, over time when you have lab scale, pilot scale, and manufacturing scale work being done, and over space where you have the chemistry or the biology of the system done in the active ingredient, then the dominant physics around the components, and then the pill finished, and then the packaging which is

the paper around it.

And if we say let's look at this over time and see what decisions we make, and over space and begin to understand why, and figure out if there is a win-win, what is the role to transform pharmaceutical manufacturing, we said those are the boxes we're going to talk about for the next few slides. What aspects of those boxes should we talk about today? And we said, let's draw a big box around all those boxes and say, let's look at pharmaceutical manufacturing and discuss it in one of those dimensions of performance.

Now when we talk about cost, that's going to be sensitive. When we talk about quality, between the regulator and the regulated there are different perceptions of cost and quality and the reasons for them. Safety is something that's universal. I think everybody is doing very well there.

And among these choices, I will decide to choose to talk about time because it means the same thing to all of us. We all have the same watch.

It's neutral. The cultural aspects, the accounting aspects, are something that we can deal with within our companies. And so the rest of my talk, I'll focus on time, but a lot of my work involves cost and quality as well. We can't do it all. Let's focus on something that we can all have a win-win on.

So let's take the simplest possible step, blending and blend uniformity as a central performance measure of that simple step that's supposed to take five minutes. And being a chemical engineer who comes from the fermentation area, when I began to focus on this five-minute step, I was really disappointed because it's such a simple step and we worry so much about it. I wanted to find out why and I wanted to find out what the opportunities were.

So the focus is only on this tiny step as an example of the possibilities over time. We look at blend process development from here to here and say, off-line, today's technology, versus on-line, tomorrow, day after tomorrow's technology. Where

is the win-win? What is it? What's stopping us now? What can we do about it?

First, it didn't seem like it was the technology itself. We were fortunate, we had a professor from the Mechanical Engineering Department who said, "Here is light, here is lasers. Let's shine them in through the blender, and I think through the window you can look at uniformity as well as that piece that you've been using for so many decades because somebody put their hands into the blender that way."

So this is MIT's duct tape technology here, not necessarily FDA-approved, on a pilot plant, through a window looking at blend uniformity. The decision is a very simple one. The question is a simple one that says, "When are we done blending?" which is "When is the relative standard deviation or the signal at the end below some number?" And the number is 6 percent, 5 percent, 4 percent, depending on where you draw the line.

But if that was the simple question, the

answer was not very disputable. We could do it very reliably, depending on where you start, what the technology is. LIF, one of our inventions, together with NIR, something that brought up together, and a lot more analytical technologies can do this very well.

The technology was easy to develop, relatively--is pretty well developed today. This is an opportunity for us to do something about it. Now what? We have something with duct tape in our labs and some of our plants. Who are we going to start talking to? What do we compare it against?

And the obvious question that says, compare it against what you have already, and that is the thiefing assay that I told you about, these rods that are put into the blender and then samples taken out physically. We know it's the thieving itself that drives the variability rather than the on-line sensor.

And then we say, "Can you compare the on-line sensor with the off-line sensor for different active concentrations to determine end point? It's

clear that on average, you can. It's clear that the new technology is less variable than the old technology.

The question then is, do I still have to use that as a benchmark to prove my new technology, when it's the old measurement that's the problem? If it is, then I'm going to have to collect a lot of data, not because it's a blend uniformity problem but because I'm comparing against an old measurement technology where the measurement is the problem.

The question then is, how do we begin to formulate if this is the right strategy for us to go forward, or we should look at the process and the product uniformity, which is really what CGMP should be all about, and we all agree it is.

So what? We have a sensor, developed pretty quickly, that's mountable technologies that are similar, can do the same thing, may be less variable. Let's figure out that it means something to all of us, as otherwise it's not worth a purely scientific exercise.

Let's define cleaning. Cleaning, yes, it's that five-minute step, but it has a lot of steps before and after it. If we want to understand "So what?" we want to understand what the consequences are on the two sides.

Blending really has these different unit operations where you clean a blender, you load a blender, you mix, you sample, you transport to a lab, and then you have a result and a decision here. You can be undermixed, mixed, or then you have to discard it if you're overmixed, and this is a new phenomenon that is quite well described within the industry, called segregation. You can actually overmix something.

The point being that while the physical process here of making something is here, the information process of measuring whether you have succeeded is far away in another functional department. When the material process is disconnected from the physical process, what is the space between the two called? It is called inventory. That's the difference between the

material process and the information process, and that's why we have all these inventory levels.

So if we were to transform from on-line to off-line technology, we have to get the information and the material flow to be in the same place. And so if we can get the on-line sensor onto the blender, on that simple operation, we can change the business processes that were talked about in the previous presentation, and we can put material information flow on the same place. We can not only do that, but once we know when to stop the blend, we can start figuring out what to do about variability within the blends.

And so we said, "This looks like it's important. It looks like it could make a difference. Let's try to figure out how big a difference it is, because the bigger the difference, more likely we would want to do it, more likely we are going to start communicating, more likely we're going to start sharing data."

And so we said, "Let's capture all of those steps," the blending steps that I told you

about, the cleaning, the charging of the active, the blending, the sampling, the QC, the decision, and the retrieving. "Let's capture all those steps, collect data from all these companies." We have a consortium, so we have a basis to collect data. "Let's try to figure out how we do it today and then ask how can you do it tomorrow."

This, for example, charge active can be modeled by each of its steps. You clean the blender and then you load the blender. You can then go inside the QC lab, and you can see you transport to the QC lab. You hold in the QC lab, you retrieve in the lab. You then prepare, test, and analyze. And then you have the people in the lab, and they're all busy moving from here to there trying to do a measurement of product uniformity based on this old technology.

Let's look at process development of just blending, now, just blend process development versus the old technology versus the new, and say, let's say that in that day, January 1, 2000, when we celebrated the new millennium, we continued, and

we do, to use the old technology. How long will it take for us to actually get a good blend, based on today's industrial practices?

And so we start the blend process development process, and you can see the blending taking place, the sampling taking place, going to the QC lab, a decision being made. Is it uniform? Is it blended? You then go to the lab and you have a different organization figuring out whether to approve it or not.

The arrow there indicating we just got our first blend below the RSD specification, and we're so excited. We look at our date, and it's the 4th of January in the morning. We started on the 1st for this 5, 10 minute operation. Now I've got one. There's this thing that says, if you can get three in a row, you're all set for the next 12 years, or at least the interpretation of it that says-- one, I've got two. All of a sudden we're not getting the third. But I got the third. It's now five days in. I go into my lab and I look at what everybody is doing.

Now you can look at what people are doing, and if it's red, it means that they're very busy, all your QC people. Now they're really busy, and they're really busy moving the samples within the lab to figure out if it's uniform. Because I'm not sure this one is going to pass, I'm going to take a few extra samples.

Since most of our analysis is based on wet chemistry rather than something you can do in the process, and most of our products are solids, you have a whole bunch of wet chemistry based HPLC equipment, red, indicating that they're very busy. We have a lot of busy equipment and people in the lab, and since we're not sure whether we're going to succeed, a lot of material information leads to a lot of samples waiting in the lab, right there.

You can go down to our plants, not just the lab, and you can say, "What are the operators doing?" Fairly busy, not fully busy, because they finished their part. They're waiting for what to do next. Blenders waiting to figure out what to do next, because they don't know the result. The

result of information is separated from the physical aspect of the actual making. And what is the difference between the two called? Inventory. That's where the period costs, all the costs show up. Now what do we do?

Well, we say we've done three. There's this argument that's a very common one. If you look at the industrial average, 27 percent is our cost of goods sold, 73 percent as a result is our gross margin. We've done three in a row. We now want to ask the question, should I do a fourth? Should I do a fifth? That would become the trade-off of time versus cost versus quality--

CHAIRMAN LANGER: Can you use the microphone?

DR. RAJU: --versus cost versus quality. The question, the common response to that is no. I've done three. I pretty much understand our process, given the technology that I have. It's now five days forward, and I'm going to go forward to do this for the next 12 years.

Now, during the next 12 years you have

another argument. It's not a time-to-market argument now, if you've been approved. It's now a cost of changes and a cost of supplements argument, and there you have this so-called cost of supplements and paperwork argument that I'll talk to you later. But before we go into manufacturing, let's stay in process development and do it right, and go back to the same date of January 2000 and see if we might learn something.

So let's go back to January 1, 2000, the same date again, and say this is exactly the same, exactly the steps. I'm not cheating here. Charging the active, loading, and cleaning. It's exactly the same date. No practices around changed. Nothing changed around cleaning, nothing changed around sampling. The only thing that has changed is you're using the on-line sensor that you took a few months or a few years to discover, although there is a lot of research that was done before it. Let's get started and see what kind of a trade-off we have across quality, time, and these competing alternatives that make our life

difficult.

So we start at the same time. It's the 1st of January. It's still the first day, and we just got our first batch. A little bit more than a day, we finished two, changing no other practices. One and a half days, we finished our three batches.

Now, how much inventory do you think we have? You've redesigned your process using technology that gave you cost, quality, and time all together. What is everybody in the lab doing? Let's look at the QC people, red indicating busy. The question then becomes, "Oh, my God, do we need those people anymore?"

[Laughter.]

And then you have the CEO, vice president, saying "What is the right head count? Can you benchmark across the industry and tell me whether it should be 20 percent or 30 percent?" And the opportunity here was, when you had the right technology, you didn't have to have that thing called QC. The same people, instead of focusing on moving samples which is a doing job, maybe could

think about the blend itself and the uniformity self, which is the process understanding job, and maybe they'll have more fun, and maybe you'll keep them a little longer, and maybe you can pay them a little more.

You just got three. You're not exactly, in removing some non value activities, potential for value-added activities, you have a whole bunch of equipment that was once busy and now is not necessarily busy.

You now have another question. You know, if it took you a day and a half to do three, maybe you can go back to those three and figure out, "You know, I'll have a higher standard." You can do four and it's still two days. Take three days, you can do five. You can do six in a little bit more than two days.

You now have done twice as many runs, you have done twice as much, maybe more, process understanding. You now have a basis to say, "I'm going to do something I understand for the next 12 years, because I chose to open my eyes, to develop

some basic technologies." What would the regulators, to make them understood and communicated? And while I think we all want together, because actually my uniformity may be better, my measurement is certainly better; I may be faster, I am; I might be cheaper, I am. And it didn't seem like anybody in this overall societal framework lost along the way.

That was product uniformity, and we can keep going forward on that. Let's skip to the next step, because I want to give you another representation as well.

If you were to look at old versus new, by looking at the business transformation of these processes based on technology, that means looking outward and deciding to work together. We have fundamentally changed the performance measures, whether you measure it as cost, quality, or time.

I said I'll focus on time because it's neutral. The impacts are not 10 percent; it's 10 times in terms of blend process development time. This is the old technology where you have one, two,

or three blenders.

Whether you do on-line technology versus off-line technology, it is not necessarily the factor of 10 improvement. It's the variability reduction, because the predictability comes when you automated and understood and then automated your processes, and there are all on that sensor right there, instead of being in a human variability of deciding whether it's Monday, Tuesday or Wednesday, and whether I'm going to wait until Monday to move my samples to the lab.

But there's an investment that has to take place across all of us to get this to happen. This is an argument of the potential, that you catalyze us to all work together to make it happen.

So this is not 10 percent here. We're talking about 10 to 15 times improvement in manufacturing. If CGMP is all about variability reduction, we get that certainly. To become independent of some of the product and organization I think would allow for a lot of generalizability beyond.

So we took a little piece called blending, it's five minutes, and we saw this huge opportunity. That was the opportunity across time. Let's look at the opportunity across space, and say let's look at routine manufacturing rather than process development, and say where is the time being spent on average, first? And if we look at 6 sigma, it's about looking at below the average, but let's start with the average. We have to simplify life. We have to start with averages because that's one number, a summary of reality at that point.

For the sake of simplicity I will not talk about the active ingredients. Since we finished this example, I'll focus on this example, and we can have so many different products once we decide to look at horizontally, and if I choose just a high volume product you might say, "You know, you forgot the others," so we look at all the different representatives and look at where time is being spent.

If you look at our processes, you'll find

they look unbelievably similar. If I go with the standard set of color coding, blue for the process steps and red for the QC testing steps, you'll find that we measure quality very much at the end. Wow, it takes a lot of time. Wow, it was pretty expensive. We don't really necessarily measure significantly in-process tests in a few places. Very rarely is there a feedback loop. We often, if you don't feel happy about something, we throw it out.

There is raw material testing. While the steps here are all about the chemistry, and this is about the physics, most of our specifications are around the chemistry, even though we really do physics afterwards. That's one argument.

The other argument is saying, given this process flow, where is my time being spent? And so let's draw that same process flow diagram in time, and you'll find here is where I'm spending my time, and here is where spending my time. And the actual process, as you saw on the previous slide, takes a lot less time than the testing itself.

Let's look at another process, so that we make sure that I'm representative, and this is the benefits of being in a consortium. Looks very similar, testing. Missing here, a lot at the end. You then say, let me open that up in time, and then you see time, and you see 60 days for just the physical formulating part of it. You see a lot of that in testing. And then you expand that out and say, "Let's include the API, and let's look at the time from the beginning to the end." And then you say, "This is close to half a year now."

Now, if I was making potato chips and it took me about half a year from the beginning to the end, I don't think I would like what I get at the end. But if it's tablets, I think clearly we have different kinds of time dimensions.

But somewhere along the way there's an opportunity to look at time. And half a year may not be necessarily the place we want to be, but let's look at the drivers behind the time. And before that, let's make sure we look at complex and liquid products, so that you are convinced that we

have looked beyond a few examples.

Here are examples of the QC time, which is the process time, in a liquid line. Here is the sterility test that totally dominates the time. And here is the testing time versus the process time, and if you were to summarize them all, in red are the testing times, in blue are the process times, six examples. Do they look similar or do they look dissimilar? The reds look very similar. The red looks very big.

Now I began to wonder whether I should have called in the MIT Pharmaceutical Manufacturing Initiative or the MIT Pharmaceutical Testing Initiative, because it seemed like all the time was being spent in testing. But is it just testing? What are the drivers behind that testing is the next question, because we've got to understand why.

And if you look at the drivers under that testing, you'll see in green is the process itself, and here is the actual test itself in blue. But all the red are the manual transfers, the interruption of the process, the securing of the

samples, the documentation, the transferring to the lab, the testing at the lab, so-called non value-added processes.

So if we were to develop technologies, it doesn't matter whether it's LIF or NIR, what is it that matters? If it's LIF or NIR, it would only impact this part of it. What really matters about any technology that we would develop is the word "on-line" rather than the words "LIF" or "NIR", because those are the ones that drive many of these paper operations. There's an investment we have to put in place to get there. It seems like it's quite a doable task. It seems like many of the technologies are very much in place.

If you then broke that detail down further, you would find that the actual test itself takes 2 percent of the time, and it's the paper aspects of the preparation before and after that takes 98 percent of the time. You've then got to say, what is the technology opportunity to deal with these, too? And that will come along the way, but that is surely not the high leverage place at

this time.

If we were to now summarize what did we learn here, quality testing is discontinuous; testing times are large; testing times are more than the process times; and it's the off-line nature of the test times that drives the overall time. The word "on-line" is a very important part of what we want to do.

Obviously we want to look beyond the average, and that's where the learning is going to begin. So let's look at those same processes that I just showed you, those six, and start looking at different aspects of the time rather than some average number of that time. And you will find that all times are not created equal, and you will find that while you will think your cycle times were 25 days or 30 days, and that's the one I showed you, there is another cluster of batches here in different colors that are totally different from everything else.

These are the so-called exception batches or variance batches. And all of a sudden something